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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,735	09/26/2003	Eric B. Kmiec	NaPro-2 CON	8506

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EXAMINER

BAUSCH, SARAE L

ART UNIT PAPER NUMBER

1634

DATE MAILED: 10/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/672,735	Applicant(s) KMIEC ET AL.	
	Examiner Sarae Bausch	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 August 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-41 is/are pending in the application.
- 4a) Of the above claim(s) 6 and 36-41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 7-35 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>06/06</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This action is in response to papers filed 08/02/2006.

Claim Status

2. Currently, claims 1-41 are pending in the instant application. Claims 1, 4, 7, 12, 15, 27, 33, and 35 have been amended while claims 6 and 36-41 are withdrawn. This action is written in response to applicant's correspondence submitted 08/02/2006. All the amendments and arguments have been thoroughly reviewed but were found insufficient to place the instantly examined claims in condition for allowance. The following rejections are either newly presented, as necessitated by amendment, or are reiterated from the previous office action. Any rejections not reiterated in this action have been withdrawn as necessitated by applicant's amendments to the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is Final.**

Withdrawn Rejections

3. The rejection of claims 1-5, 7-21 and 27-35 under 35 USC 112, second paragraph, made in section 5 of the last office action mailed 05/05/2006 is withdrawn in view of the amendment to the claims.
4. The rejection of claim 4 under 35 USC 112, first paragraph, made in section 7 of the last office action mailed 05/05/2006 is withdrawn in view of the amendment to the claims.
5. The rejection of claim 1, 3-5, 7, 9-12, 14-21, 27, and 29-35, under 35 USC 102(b), made in section 9 of the last office action mailed 05/05/2006 is withdrawn in view of the amendment to the claims.

New Grounds of Rejections

Claim Rejections - 35 USC § 112- New Matter

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-5, 7-21, and 27-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The recitation of “free of a recombinase” is not supported in the specification and raises the issue of new matter. The specification discloses adding a second oligonucleotide, an annealing oligo, to a RecA stabilized d-loop complex (see figure 1 and example 1, page 31, lines 5-18) and the specification further teaches the second oligonucleotide does not substantially bind a recombinase (see page 5, lines 11-20, for example); however the specification does not teach contacting the sample with a first oligonucleotide bound by a recombinase and a second oligonucleotide free of a recombinase. The specification does not teach contacting the sample with a second oligonucleotide free of a recombinase. The specification does teach adding to the RecA stabilized d-loop complex an annealing oligo that is free of recombinase but does not teach contacting the sample with a first oligonucleotide bound by a recombinase and a second

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oligonucleotide free of a recombinase. The specification is limited to the *addition* of a second oligonucleotide free of a recombinase to the RecA stabilized d-loop complex.

Furthermore, example 1 teaches a method in which a first oligonucleotide is mixed with a recombinase and a double stranded target nucleic acid is added and then a second oligonucleotide is added, however the specification does not appear to provide support for methods in which a first oligonucleotide bound by a recombinase and second oligonucleotide free of a recombinase are contacted with a sample. The specification on page 5 characterizes the second oligonucleotide as incapable of substantially binding a RecA-like recombinase but does not appear to provide support for the distinct concept of a second oligonucleotide free of a recombinase as the phrase “second oligonucleotide free of a recombinase” encompasses both oligonucleotides that are added to the reaction mixture without the addition of the recombinase and the oligonucleotides that do not bind or are not associated (directly or indirectly) with a recombinase. The teachings that the second oligonucleotide does not substantially bind a recombinase does not provide support for these embodiments. In particular, the specification as originally filed does not appear to provide support for the concept that the second oligonucleotide is not capable of binding any recombinase.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. Claim 1-5, 7-21, 23, and 27-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sena et al. (US Patent 5670316 Sept 1997) in view of Bryant et al. (PNAS 1985, vol. 82, pp. 297-301). This rejection was previously presented in section 11 of the office action mailed 05/05/2006 and has been extended to the newly amended claims.

Sena et al. (US Patent 5670316) teach a method of detection and isolating a linear duplex DNA having a first and second strands, containing a first internal DNA target sequence (where duplex DNA analyte present in a mixture of nucleic acid molecules) (see column 5, lines 55-57). Sena et al. teach a set of two DNA probes provided, having a first and second probe strands, where the first and second probe strand contain complementary sequence to the first and second target sequence strands and contain complementary overlap between the probe strands (see column 5, lines 55-60). Sena et al. teach the probes coated with RecA protein and combined with the linear duplex DNA which contains the target sequence under conditions that produce a probe: target complex containing the probe strands and both target strands which is stable to deproteinization (see column 5, lines 60-67). Sena et al. teach separating the mixture of nucleic acid molecules from the probe: target complex (see column 6, lines 2-7). Sena et al. teach the detection method can be applied to the detection of duplex DNA in any nucleic acid sample and further can be used in applications of clinical diagnosis of infection diseases to include diagnosis of certain genetic diseases caused by specific deletion/mutation, insertions, or rearrangements in mammalian DNA (see column 15, lines 24-26 and 29-30). Sena et al. does not teach a second oligonucleotide that is recombinase-free.

Bryant et al. teach a method of renaturation of complementary DNA strands by recA protein. Bryant et al. teach that higher levels of RecA protein markedly reduced the rate or

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renaturation (see page 298, 2nd full paragraph). Bryant et al. further teach renaturation reaction promoted by RecA protein proceeds optimally at levels of RecA protein sufficient to cover 10-15% of the DNA and RecA protein levels that are sufficient to approach saturation of the DNA strands produce a marked decrease in the efficiency of renaturation (see page 300, 1st full paragraph, 2nd column). Bryant et al. teach that similar conclusions were reached on the analysis of RecA protein-promoted D-loop formation (see page 300, 1st full paragraph, 2nd column).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of detection and isolating a linear duplex DNA using RecA coated probes to form a double D-loop complex by Sena et al. to include only the first probe coated with RecA and second probe without any RecA bound because saturation of DNA strands with RecA produce a marked decrease in the efficiency of hybridization as taught by Bryant. The ordinary artisan would have been motivated to improve the method of coating both first and second probe with RecA as taught Sena et al. with the method of reducing the amount of RecA as taught by Bryant et al. because Bryant teaches that optimal levels of RecA for hybridization cover only 10-15% of the DNA and saturation levels of RecA coating DNA strands decrease the efficiency of renaturation. The ordinary artisan would have had a reasonable expectation of success that the use of coating only the first single stranded probe with RecA could be used in the method of Sena et al. because Bryant et al. teach that similar conclusions of less RecA mechanisms of binding were seen in d-loop formation.

Response to Arguments

10. The response traverses the rejection on page 14-15 of the response mailed 08/02/2006. The response asserts that there is no motivation or suggestion in Bryant et al. regarding

renaturation using RecA-free renaturation techniques nor would there be as Bryant is directed to RecA promoted renaturation. The response asserts that there is no motivation that Sena et al. be modified to remove recombinase from one of the DNA probes because RecA is known to promote renaturation. The response asserts that Bryant does not address recombinase-free renaturation and teaches away from this concept because it is directed to recombinase promoted renaturation. This response has been thoroughly reviewed but not found persuasive. It is unclear what applicant is verifying to by "renaturation". The claims are drawn to producing a double D loop in the presence of a recombinase and it is unclear if applicant is referring to the formation of the double D loop as renaturation or perhaps strand exchange in the presence of RecA as renaturation. Renaturation generally refers to formation of a duplex or conversion of denatured DNA to its native configuration and none of the claims require formation of a duplex or denatured DNA converting to its native configuration. Furthermore, none of the claims recite a method of double D loop formation without recombinase. However, if applicant is referring to renaturation as formation of a double D loop, both Sena et al. and Bryant et al. teach the use of RecA in the formation of D loop structures and Bryant teaches that optimal levels of RecA for hybridization cover only 10-15% of the DNA and saturation levels of RecA coating DNA strands decrease the efficiency for D loop formation (see page 300). The ordinary artisan would have been motivated to use less RecA and have one strand free of a recombinase for optimal hybridization conditions.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Maintained Rejection

Claim Rejections - 35 USC § 112- Second Paragraph

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 22-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection was previously presented in section 5 of the last office action mailed 05/05/2006 and is reiterated below.

(a). Claims 23 recites the limitation "said second, recombinase-free oligonucleotide" in line 3 of the claims. There is insufficient antecedent basis for this limitation in the claim. Claims 23 depend on claim 22 and claim 22 does not recite a second oligonucleotide that is recombinase-free. Claim 22 recites "second oligonucleotide is not substantially bound by a recombinase", however this recitation does not limit the second oligonucleotide to be recombinase-free and as such claim 23 lack antecedent basis.

(b). The term "substantially" in claim 22 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear if "not substantially bound" means the second oligonucleotide is not bound to RecA, the second oligonucleotide is bound transiently to RecA, the second oligonucleotide is only bound to certain regions of RecA,

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RecA only bound to certain regions of the second oligonucleotide or is the second oligonucleotide affinity to RecA less than the affinity of the first oligonucleotide to RecA.

Claims 23-26 depend from claim 22 and are therefore indefinite for the reasons applied to claim 22.

Response to Arguments

13. The response asserts on page 13 of the response mailed 8/2/2006 that in view of the amendment to the claims, the rejection no longer applies. However, claim 22 and 23 were not amended and therefore the rejection still applies to these claims. For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 22 and 24-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Sena et al. (US Patent 5670316 Sept 1997). The phrase “is not substantially bind” is being interpreted to encompass that some RecA is bound to the second oligonucleotide.

With regard to claim 22, Sena et al. teach a method of detection and isolating a linear duplex DNA having a first and second strands, containing a first internal DNA target sequence (see column 5, lines 55-57). Sena et al. teach a set of two DNA probes provided, having a first and second probe strands, where the first and second probe strand contain complementary

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sequence to the first and second target sequence strands and contain complementary overlap between the probe strands (see column 5, lines 55-60). Sena et al. teach the probes coated with RecA protein and combined with the linear duplex DNA which contains the target sequence under conditions that produce a probe: target complex containing the probe strands and both target strands which is stable to deproteinization (producing a stabilized double D loop) (claim 1) (see column 5, lines 60-67). Sena et al. teach separating the mixture of nucleic acid molecules from the probe: target complex (detecting stabilized double D loop) (purifying double stranded nucleic acids) (see column 6, lines 2-7). Sena et al. teach the detection method can be applied to the detection of duplex DNA in any nucleic acid sample and further can be used in applications of clinical diagnosis of infection diseases to include diagnosis of certain genetic diseases caused by specific deletion/mutation, insertions, or rearrangements in mammalian DNA (see column 15, lines 24-26 and 29-30).

With regard to claim 24, Sena et al. teach deproteinization after RecA catalyzed homologous probe: target reaction for 15-20 min. at 37°C (see column 30, lines 36-42).

With regard to claim 25-26, Sena et al. teach the use of methylated probes to detect target and form double d-loop complex (see column 22, lines 39-44). Sena et al. teach the use of ³²P- and biotin-labeled 121-mer probe strand (claim 26) (1st and 2nd oligonucleotide probe complementary to target sequence (see column 13, lines 50-53). Sena et al. teach direct labeling of probe strands with fluorescent moieties like fluorescein-11-dUTP (see column 21, lines 57-60).

Response to Arguments

16. The response asserts on page 14 of the response mailed 8/2/2006 that the phrase "does not substantially bind recombinase" has been deleted from the claims and as such Senat et al. does not teach a second oligonucleotide free of recombinase. This response has been thoroughly reviewed but not found persuasive because claim 22 was not amended and therefore the rejection still applies to these claims. For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 1-5, 7-26 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-67, 72-78 of copending Application No. 10/260150. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 1-5 and 7-26 are generic to all that is recited in claims 1-67, 72-78 of copending application no. 10/260150. Claims 1-2, 55-56, 63-34, 72, and 76 of '150 fall entirely in the scope of instant claims 1, 7, 12, 15, 22 comprising a

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method producing a double d-loop and detecting the presence of a desired target sequence with formation of a double d-loop with two oligonucleotides and the invention of instant claims 2-5, 8-11, 13-14, 16-21, and 23-26 are recited in dependent claims 3-49, 21-24, 32, 37-40, 47-48, and 61.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Argument

19. The response submits on page 15-16 of the response mailed 08/02/2006 that should application 10/260150 issue with the same claims as set forth, applicant would file a terminal disclaimer. As such, this rejection will be maintained until such time.

Conclusion

No claims are allowable.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

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CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 9am-5pm.

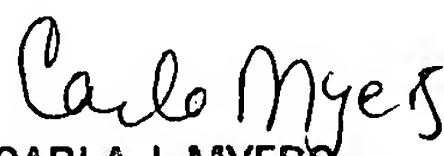
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

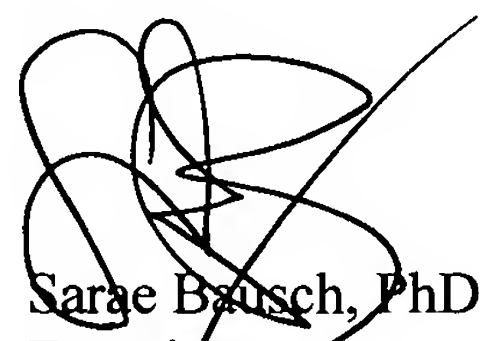
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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.


CARLA J. MYERS
PRIMARY EXAMINER


Sarae Bausch, PhD.
Examiner
Art Unit 1634